REMARKS

This paper is being filed in response to the Final Office Action dated February 25, 2004 along with a Request for Continued Examination. The claims currently pending are claims 40, 54, 61-65, 72-75, 82-86, 93 and 94.

Applicants acknowledge, with appreciation, the Examiner's withdrawal of the rejections of the drawings and to the Specification.

Applicants also acknowledge that the rejection of claims 93-96, and 98-101 have been rendered moot.

Applicants gratefully acknowledge withdrawal of the rejection of claims 40, 54, 61-65, 72-75, and 82-86 under 35 U.S.C. §112, second paragraph.

Applicants renew their statement that a terminal disclaimer over U.S. Serial No. 09/921,157 will be submitted upon receipt of an indication of allowability.

35 U.S.C. §112, second paragraph

The Office Action maintains the rejection under 35 U.S.C. §112, second paragraph as being indefinite due to the inclusion of the word "substantially" and the phrases "substantially no toxicity" and "substantially reduced toxicity." While not conceding the correctness of the Office Action, Applicants herein amend claims 40, 63, 74 and 84 to remove the word "substantially." Therefore, the rejection that the degree of toxicity is unclear is obviated.

With respect to "toxicity" encompassing all forms of toxicity, including, for example, "cytotoxicity, endotoxicity, exotoxicity, cell-vacuolizing toxicity," Applicants invite the Examiner's attention to the Specification at page 5, lines 35-39, wherein it is described that the protein has "cytoxic [*sic*] activity." (Note that the typographical error is corrected herein). Furthermore, the cytotoxin causes vacuolization and death of a number of cell types. Thus, for clarity, the Applicants herein amend the claims to recite "no cytotoxic activity or reduced cytotoxic activity." This is specifically defined under the definition of cytotoxin, and would be easily understood by one of skill in the art reading the Applicants' specification.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. §112, first paragraph (New Matter)

The Office Action maintains the rejection under 35 U.S.C. §112, first paragraph as allegedly containing new matter. Applicants respectfully disagree.

The Applicants disclose polypeptides of SEQ ID NO:3, that, when used as immunogens, elicit antibodies in animals that also recognize the native cytotoxic protein of *Helicobacter pylori*. The Examiner states in the Office Action "A non-recombinant polypeptide present in the protein extracts of a cytotoxin-producing strain of *H. pylori* is expected to be fully cytotoxic, as opposed to be substantially non-cytotoxic." (Office Action dated February 25, 2004, page 6, lines 13-14). However, the Applicants are not claiming that the native protein is non-cytotoxic, as the statement suggests, but that the *polypeptides of the invention* (useful as immunogens) are non-cytotoxic or have reduced cytotoxicity. The claim language includes the feature that the polypeptides of the invention are immunologically identifiable by antibodies that react specifically with the polypeptide having the amino acid sequence of SEQ ID NO:3 (*i.e.*, the same antibodies recognize the polypeptides as recognize the native protein having the amino acid of SEQ ID NO:3) and that the polypeptides exhibit no toxicity or reduced toxicity.

Moreover, the specification teaches at page 14, lines 21-30 that the polypeptides of the invention consist of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably at least 11-15, or which is immunologically identifiable with a polypeptide encoded in the [designated] sequence." Thus, there is direct support for the phrase within the claims. The originally filed claims and the specification (amended to include the language of the originally filed claims) specify that the polypeptides of the invention exhibit substantially no toxicity or substantially reduced toxicity (see original claim 8, as filed and the amended specification at page 4 lines 1-4). Thus, no new matter is added.

Prompt withdrawal of the rejection is respectfully requested.

35 U.S.C. §112, first paragraph ("Written Description")

The Office Action maintains the rejection under 35 U.S.C. §112, first paragraph ("Written Description").

In *In re Wertheim*, the court noted that "the function of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter *later* claimed by him" *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976).

The Office Action appears to addresses the issue of later claiming. The Office Action states:

> The genetic detoxification alluded to in the Del Giudice Declaration was not contemplated in the instant specification, as originally filed. Nowhere in the specification can one find the direction and guidance to produce detoxified cytotoxins of *Helicobacter pylori*, or their fragments of the recited length, such that they possess substantial non-cytotoxicity, or substantially reduced cytotoxicity and at the same time remain immunolgically identifiable by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin of SEQ ID NO:3.

Applicants respectfully disagree. Essentially, the Examiner states that there is no support for the following:

(A) cytotoxin fragments of the recited length

(B) possessing substantially no or reduced cytotoxicity

(C) immunologically identifiable by antibody that reacts with cytotoxin

The Applicants teach at page 14, lines 21-30 that the polypeptides of the invention consist of at least 3-5 amino acids, and more preferably at least 8-10 amino acids, and even more preferably at least 11-15, or which is immunologically identifiable with a polypeptide encoded in the [designated] sequence." The specification also teaches that the antibodies raised against a portion of SEQ ID NO:3, including a 23 amino acid region of SEQ ID NO:3, recognize a 100 kDa protein that co-purifies with vacuolating activity from cytotoxin positive, but not cytotoxin negative strains of *Helicobacter pylori* (Specification at page 47, lines 10-30). The passages of the specification show that the Applicants had possession of a

fragment of the cytotoxin of the recited length (Part A) that elicited an antibody response in which the antibodies also recognized the native protein of SEQ ID NO:3 (Part C). As for Part B, claim 8, *as originally filed*, specifically states that the recombinant protein (which includes a derivative or fragment thereof with reference to claims 1 and 2) "exhibits substantially no toxicity, or substantially reduced toxicity." This point is conceded by the Examiner in the Office Action at page 10, lines 12-14 ("It should be noted that the only place where the phrase 'substantially no toxicity' or 'substantially reduced toxicity' was mentioned in the specification as originally filed was in some original claims"). Applicants note that the claims as filed form part of the disclosure and according to the MPEP:

> The claims as filed in the original specification are part of the disclosure and, therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985). Thus, the written description requirement prevents an applicant from claiming subject matter that was not adequately described in the specification as filed.
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> MPEP 2163.06 III at p. 2100-183.

The Applicants have previously amended the Specification to include the language "substantially no toxicity" and "substantially reduced toxicity." Thus, there is full support in the specification for the terms, and all parts of the claimed invention are supported by the disclosure. In other words, there is no later claiming issue with regard to the instant claims.

With regard to the description not providing guidance as to producing genetically detoxified toxins, the Office Action states that the genetic detoxification was not contemplated in the originally filed specification and rejects the statements of the Del Giudice Declaration as addressing pertussis toxin while not addressing the "unpredictability" factor. Applicants believe that the Office Action misses the point of the Declaration.

The Del Giudice Declaration refers to genetic detoxification of toxins as an art-recognized technique at the time of filing. The law makes clear that "not everything necessary to practice the invention needs to be disclosed. In fact, what is well-known is best omitted." *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP § 2164.08. One of skill in the art, when faced with making the immunogenic portions of the SEQ ID NO:3 cytotoxin

having substantially no, or reduced toxicity would look to the art to achieve this goal, and would rely on such techniques as disclosed in Pizza *et al.* (1989) "Mutants of pertussis toxin suitable for vaccine development" *Science* 246:497-500 (Del Giudice Declaration, paragraph 9). The Specification provides guidance to use techniques to modify the polypeptides of the invention at page 8, lines 13-23 wherein it is taught that in using recombinant polynucleotides, mutagenesis may be used to produce one or more altered polypeptides.

The Examiner concedes that one may be able to produce fragments of SEQ ID NO:3 and test their cytotoxicity and immunological identifiability. The Examiner, however, believes that "given the art-disclosed conformational complexity and functional unpredictability, the maintenance of immunological identifiability by an antibody specifically reactive with the native cytotoxin polypeptide of SEQ ID NO:3 along with the concurrent recited attenuation in cytotoxic activity following one or more amino acid substitutions in the cytotoxin polypeptide, would not have been predictable." (Office Action of February 25, 2004, p. 9, lines 3133 through p. 10, lines 1-3).

The Office Action characterizes the Manetti reference as teaching the conformational complexity of a *Helicobacter pylori* cytotoxin polypeptide, and "[e]ven partial destruction of the conformational epitopes by chemical inactivation can result in lowering of the effective immunogenicity." However, the complexity of the conformation of the protein also likely affects toxicity. That is, the destruction of the conformational structure, such as by making fragments of SEQ ID NO:3, would likely produce polypeptides of reduced or no toxicity. Further, the claims require only that the antibodies raised against the fragments recognize the native protein, which could be useful in therapeutic *or diagnostic* applications. One of skill in the art, as conceded by the Examiner, may be able to test for immunological identifiablilty. Further, in the above quoted passage, Manetti referred to destruction of epitopes by chemical inactivation, not genetic detoxification. With respect to genetic detoxification, Manetti recognized the value of detoxified *H. pylori* cytotoxin after the Applicants in the instant application. Manetti's failure to recognize in 1995 that Applicants had already sought patent protection for an invention drawn to the same subject matter is immaterial to the adequacy of written description.

The Applicants have submitted ample evidence of conception of the invention and have provided a constructive reduction to practice with the filing of a patent application.

Moreover, the application contains a written description of the invention evidencing that the Applicants had possession of the invention at the time of filing. Applicants earnestly submit that the specification, which contains an actual reduction to practice in the form of eliciting antibodies to a portion of SEQ ID NO:3 that recognizes the native cytotoxin, also provides evidence that the requisite means and their interaction was comprehended.

Withdrawal of the rejection under 35 U.S.C. 112, first paragraph is respectfully requested.

35 U.S.C. §102

The Office Action maintains the rejection of claims 40, 54, 61-65, 72-75, 82-86, 93 and 94 under 35 U.S.C. §102 (e) as anticipated by U.S. Patent No. 6,054,132 to Cover *et al.* ("COVER I") and under 35 U.S.C. §102 (b) as anticipated by Cover *et al.* (1992) *J. Biol. Chem.* 267:10570-10575 ("COVER II").

The instant application is a divisional of U.S. Serial No. 08/466,662 filed June 6, 1995, which is a divisional of U.S. Application No. 08/256,848, filed October 21, 1994, which is a U.S. National Phase of PCT/EP93/00472, filed March 2, 1993 and PCT/EP93/00158, filed January 25, 1993, which two PCT Applications claim benefit of Italian application No. FI 92 A 000052, filed March 2, 1992.

To clarify the previous response regarding COVER II as not constituting prior art, Applicants note that COVER II was published May 25, 1992 (two months *after* the Applicants' priority date for the Italian Application and less than one year prior to the PCT applications). As the Applicants believe they have fully addressed the new matter rejection in this Response, and are thereby entitled to the earliest claim of priority, Applicants respectfully submit that COVER II does not quality as prior art under 35 U.S.C. §102(b). However, to the extent that the Examiner believes that COVER II may qualify as prior art under another subsection of 35 U.S.C. §102, Applicants will address the application of COVER II against the claims as well.

COVER I discloses the purification of a cytotoxin of *Helicobacter pylori* with vacuolating activity. COVER I specifically states at Col. 2, lines 7-9 "It is an object of the present invention to provide a substantially pure antigenic composition *with vacuolating toxin activity*" (emphasis added). Further the patent states that one embodiment of the invention is

"a purified antigenic composition *with vacuolating toxin activity* (hereinafter termed CB antigen)" and the term CB antigen is defined as the "functionally active non-denatured vacuolating toxin" (col. 2, lines 37-39). Thus, COVER I does not teach or suggest the use of portions of the cytotoxin that exhibit substantially no, or substantially reduced cytotoxicity as claimed in the instant application.

The Office Action appears to believe that the Patent teaches a 23 amino acid fragment of the CB toxin which comprises the antigenic polypeptide. This is incorrect. The Patentees performed N-terminal sequencing on a purified toxin to deduce the amino acid composition and sequence of the N-terminus of the toxin. This portion was not used as an immunogen, rather, it was performed to partially characterize the entire CB toxin. The Examiner concludes:

> [t]hat the structurally identical 23 amino acid-long antigenic polypeptide of the prior art obtained from a purified toxin, is pure enough to be of substantially no endotoxicity, or of substantially reduced LPS-related toxicity and is long enough to be immunologically identifiable by antibodies specific to the amino acid sequence of SEQ ID NO:3 are inherent from the teachings of [COVER I]

However, as described above, this is simply factually incorrect, and therefore unfounded. COVER I did not obtain and purify a 23 amino acid fragment from the toxin. Such is neither the purpose nor the result of N-terminal sequencing.

Thus, COVER I does not teach every element of the claims and does not anticipate the claims within the meaning of 35 U.S.C. §102.

Likewise, COVER II teaches the purification to homogeneity of a vacuolating cytotoxin from *H. pylori*. One step in evaluating the purified protein in COVER II was to perform N-terminal amino acid sequencing to determine the amino acid sequence of the first 23 amino acids. Notably, COVER II did *not* purify a fragment of the cytotoxin comprising 23 amino acids. Amino acid sequencing breaks the peptide bond of the N-terminal amino acid and analyzes it, and subsequently the next amino acid is cleaved from the peptide chain. Thus, COVER II does not include every limitation of the claims and does not anticipate the claims within the meaning of 35 U.S.C. §102.

Withdrawal of the rejections under 35 U.S.C. §102 is respectfully requested.

Conclusion

Applicants respectfully request reconsideration in view of the foregoing amendments and remarks and urge prompt allowance of the claims.

Respectfully submitted,

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